REMARKS

Reconsideration of this application, as amended, is respectfully requested

I. Status Of The Claims:

Claim 21 was amended to correct for a typographical error. Claims 21 to 25, 31, 33 to 35, and 41 to 45 are pending in this application. No new matter has been added to the application as a result of the present amendment.

II. Information Regarding Other Applications

The Applicants wish to draw the Examiner's attention to recently issued U.S. Patent No. 6,989,232. The published PCT counterpart application (WO 02/16599) of this patent was already cited in the Applicants' Second Supplemental information disclosure statement dated June 2, 2003..

III. Associate Power of attorney

Applicant submits herewith an associate Power of Attorney for Emily Miao, Anita J. Terpstra, and Paul H. Berghoff of the law firm of McDonnell Boehnen Hulbert & Berghoff (Customer no. 020306) from an attorney or agent of record. Accordingly, Emily Miao is now an attorney of record via the associate Power of Attorney document.

IV. Rejections under 35 U.S.C. § 101

Claims 21-25, 31, 33-35 and 41-45 stand rejected under 35 U.S.C. section 101, because the claimed invention allegedly lacks patentable utility. Specifically, the Examiner alleges that the claims lack support for either a specific or substantial utility for reasons described in detail on pages 2 and 3 of the Advisory action and pages 2 and 3 of the Office action dated December 27, 2004. Applicants stand by their previous amendments and remarks in their prior Rule 116 response dated June 27, 2005 and further provide the following discussion to assert the specific and substantial utility of the claimed invention.

To properly reject a claimed invention under 35 U.S.C. 101, the Examiner must (A) make a *prima facie* showing that the clamed invention lacks utility, and (B) provide sufficient evidentiary basis for factual assumptions relied upon in establishing the *prima facie* showing. A *prima facie* showing must establish that it is more likely than not that a person of ordinary skill in the art would

not consider that any utility asserted by the applicant would be specific and substantial. The *prima facie* showing must contain the following elements:

(1) An explanation that clearly sets forth the reasoning used in concluding that the asserted utility for the claimed invention is not both specific and substantial nor well-established;

(2) Support for factual findings relied upon in reaching this conclusion; and

(3) An evaluation of all relevant evidence of record, including utilities taught in the closest prior art.

Further, whenever possible, the Examiner should provide documentary evidence regardless of publication date (e.g., scientific or technical journals, excerpts from treatises or books, or U.S. or foreign patents) to support the factual basis for the *prima facie* showing of no specific and substantial credible utility. If documentary evidence is not available, the Examiner should specifically explain the scientific basis for his or her factual conclusions.

Applicants submit that the Examiner has failed to make a *prima facie* showing of lack of utility because the Examiner has failed to satisfy paragraph (3) of the required elements. While the Examiner makes various factual allegations that the claimed invention lacks specific and substantial utility, it fails to fully consider all of the teachings in the references cited by the Applicants, particularly in support of the asserted utility. Thus, the Examiner has not met the initial burden of showing more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the Applicants would be specific and substantial.

Specific Utility

An invention has specific utility if the identified use or application is specific to the subject matter claimed. As explained in the specification, one of the cardinal features of lymphocyte activation is the involvement of distinct signaling cascades which in turn involve specific adaptor proteins. Applicants' hSLAP-2 is believed to be a new member of the SLAP family adapter proteins and acts as a negative regulator of intracellular signal transduction in several cell types, including T-cells. Thus, claims to the nucleic acid sequences of hSLAP-2 as well as a method for making isolated hSLAP-2 have a specific utility in that it can be used for diagnosis, screening, monitoring, therapy, and prevention of immune system related conditions or diseases.

The Examiner has consistently alleged that the utility of a protein cannot be demonstrated by showing that a protein is homologous to another protein that has a well-known utility, citing to Whisstock for support. Applicants point out that this argument is clearly erroneous in consideration of the fact that Applicants correctly identified the sub-family of adaptor proteins to which hSLAP-2 belongs, correctly identified the physiological function of the hSLAP-2 protein, and correctly identified the mechanism by which hSLAP-2 mediates its function, as taught by Applicants specification as originally filed. Moreover, the fact that Pandey, Holland, Loreto, and McGlade all ascribe the same family and functional assignments to hSLAP-2 using the same homology criteria as Applicants also clearly demonstrates that this type of association is well-established and commonly accepted in the art.

Applicants do not refute the teachings of Whisstock, however Applicants assert that the Examiner's allegation that "prediction of protein function from sequence and structure is a difficult problem" is moot considering exceptions to this difficulty clearly exist which as evidenced by the teachings of Applicants specification. The Examiner alleges that "[e]ven in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein". Applicants disagree and point to the teachings of Applicants specification again as evidence that experimental research is not required to accurately predict protein function. Nonetheless, the teachings of Pandey, Holland, Loreto, and McGlade and the Declaration of Gina S. Whitney, discussed below, do provide such experimental confirmation and thus the Examiner's allegation is moot.

After establishing the strong supporting evidence that hSLAP-2 is a new member of the SLAP family of adapter proteins, Applicants also pointed out the utilities for hSLAP-2 as disclosed in Applicants specification. Specifically, Applicants pointed out that the specification teaches that the hSLAP-2 polypeptide is an adaptor protein which functions "in the receptor-ligand signal transduction pathway in cells of the hematopoietic lineage" (see paragraph 54 of specification). More particularly, Applicants specification teaches that hSLAP-2 is a "negative regulator[s] of intracellular signal transduction in several cell types, including T-cells" (see paragraph 76). Applicants specification also teaches that hSLAP-2 is useful for "the diagnosis, screening, monitoring, therapy, and prevention of immune system related conditions or diseases, particularly those involving T-cell and B-cell neoplasms; inflammation disorders, diseases and conditions, rheumatoid arthritis, osteoarthritis, psoriasis, rhinitis, inflammatory bowel disease (Crohn's and

ulcerative colitis), allergies, particularly those involving hyperactivity of B-cells and T-cells, or other immune cells, such as mast cells or eosinophils; autoimmune diseases such as systemic lupus erythematosus and multiple sclerosis; pulmonary diseases including asthma, acute respiratory distress syndrome, and chronic obstructive pulmonary disorder; tissue/ organ rejection; and cancer" (see paragraph 12).

Applicants also referred the Examiner to three post-filing publications from three independent groups, namely Pandey, Holland, and Loreto, that completely corroborated the teachings of Applicants specification relating to the description of hSLAP-2 as a new member of the SLAP family of adaptor proteins, in addition to its utility as a negative modulator of T-cell activation. Specifically, Pandey, Holland, and Loreto identified a protein identical to hSLAP-2, recognized hSLAP-2 as representing a new member of the SLAP family of adapter proteins using the same criteria utilized by Applicants (e.g., percent homology, shared structural features, etc.), and established experimentally that hSLAP-2 functions as originally conceived in Applicants specification (e.g., as a negative modulator of T-cell activation).

Applicants also pointed out to the Examiner that the instant specification teaches that hSLAP-2 is capable of binding to ZAP-70 and that one skilled in the art would appreciate that any molecule that binds to ZAP-70 would be expected to affect T-cell receptor signaling and thus would be useful as a target for therapeutic intervention for disorders affecting T-cell antigen receptor signaling, such as T-cell tumors, lymphomas, leukemias, thymomas, and autoimmune disorders, among others (see paragraph 9). This rational is supported by the teachings of Chen; Zhang; Chan; Williams I; and Williams II and is based upon the fact that ZAP-70 links the activated T-cell receptor to downstream signaling events that ultimately leads to the transcription of genes such as IL-2, which is a hallmark of T-cell activation.

Both Pandey and Loreto demonstrate experimentally that hSLAP-2 is capable of binding to ZAP-70 and teach that this is the mechanism by which hSLAP-2 negatively affects T-cell receptor activation. Applicants believe this information alone demonstrates that hSLAP-2 has a well-established utility and was specifically taught by the teachings of Applicants specification.

The Applicants further draw the Examiner's attention to the attached Declaration of Gina S. Whitney, an employee of the assignee, with accompanying Exhibits A-C. As Ms. Whitney has stated, she had performed or directed an experiment to be performed to provide evidence that

hSLAP-2 inhibits anti-human CD3 antibody mediated NFAT promoter activation in Jurkat cell line. Her experiment was based on work that was performed and reported by others subsequent to the filing date of this application. See Loreto; and McGlade. Jurkat/ NFAT promoter -luciferase cells was transiently transfected with 20 μg and 40 μg of SLAP-2_GFP or a control_GFP DNA and its effect was examined on luciferase activity 40 hours post-transfection and after stimulation with anti-human CD3 antibody for six hours. Transfection efficiency was measured by FACs analysis (Figure 1). As shown in Figure 2. SLAP-2 inhibits anti- human CD3 antibody mediated NFAT promoter activation in a Jurkat cell line.

The results of Ms. Whitney's experiment support the original teachings of the subject application, namely that (i) hSLAP-2 is a member of the SLAP family of adapter proteins which function in receptor-ligand signal transduction pathway in cells of the hematopoietic lineage; and (ii) that SLAP-2 is a negative regulator of intracellular signal transduction in several cell types, including T-cells. See paragraphs 54 and 76 of the specification. The results of her experiment are also consistent with other findings that show that overexpression of hSLAP-2 regulates T cell receptor signaling. See Loreto, McGlade, Pandey, and Holland. Ms. Whitney's results support that hSLAP-2 negatively modulates T-cell receptor activity.

Thus, as Applicants had pointed out to the Examiner previously, the utility of hSLAP-2 is "specific" since modulation of T-cell receptor activation is specific to methods of treating and/or diagnosing immune disorders specific to aberrant T-cell receptor activity since "unregulated activation of the T-cell receptor (TCR) can lead to aberrant T-cell growth, resulting in, for example, T-cell tumors, lymphomas, leukemias and thymomas" (see Applicants August 18th, 2003 Reply, page 12). Since one of the utilities of hSLAP-2 relates to methods of treating aberrant T-cell receptor disorders, the Examiner is reminded that asserting the utility rejection on this basis is not in accordance with the guidance provided in the Revised Interim Utility Guidelines since "most diseases or conditions can be treated, rejections under 35 U.S.C 101 for treatment claims should rarely be made".

Substantial Utility

A claimed invention has substantial utility if it defines a "real world" use. According to the MPEP, "any reasonable use that an applicant has identified for the invention that can be viewed as

providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial' utility". MPEP §2107.01 I. The term "benefit to the public" is not interpreted "to mean that products or services based on the claimed invention must be 'currently available' to the public in order to satisfy the utility requirement." MPEP §2107.01, citing *Brenner v. Manson*, 383 U.S. 519, 534-35 (1966).

Applicants point out that since hSLAP-2 has been shown to negatively regulate T-cell receptor (TCR) signaling, it automatically implicates hSLAP-2 as functioning in the co-stimulatory pathway. As the Examiner will appreciate, in order for T-cells to be fully activated they require two signals, the first from the T-cell receptor itself, and the second from a costimulatory signal such as CD28 or CTLA-4. This costimulatory signal provides an amplification of the TCR signal which enables the T-cell to proliferate ultimately leading to the production of cytokines including IL-2, as described *supra*. In addition to the positive costimulatory signal delivered by CD28, a negative signal is provided via CTLA-4 which inhibits T-cell activation, proliferation and cytokine production. The balance between CD28 and CTLA-4 expression determines whether the T-cell will be activated or not.

In cancer patients, or animals with tumors, it is known in the art that the host immune system is suppressed and T-cell responses are diminished thus enabling the cancer to evade recognition by the immune system and continue to proliferate. Therefore, one well-established approach to treating cancer is disruption of the co-stimulatory pathway – an approach known as immunomodulatory therapy. Leach described an antibody directed against CTLA-4 which has been used to activate the immune system. These types of antibodies block CTLA-4 function, thereby, stimulating T-cell proliferation and function. Studies from the Leach group have shown that an anti-CTLA-4 antibody has anti-tumor activity in animals and clinical studies are ongoing with similar types of molecules. Therefore, by analogy, since hSLAP-2 acts to attenuate immune responses, an antagonist directed against hSLAP-2 would similarly be expected to have anti-tumor activity largely due to disruption of ZAP-70 binding and thus amplification of T-cell receptor activation.

Disruption of the co-stimulatory pathway is also a well-known mechanism for treating various immune disorders. CTLA4-Ig is an Ig fusion protein that has been shown to potently inhibit T-cell proliferation in vitro, like hSLAP-2 (see Tan;), in vivo (see Webb and Finck), and in human subjects (see Kremer) and is currently an FDA-approved therapy for the treatment of rheumatoid

arthritis. Clearly, one skilled in the art would recognize that hSLAP-2, a protein that affects the same co-stimulatory pathway, would reasonably be expected to have the same utility as CTLA4-Ig.

Applicants also pointed out that the utility of hSLAP-2 represents a "substantial" utility and does not constitute a throw-away utility since its use in treating and/or diagnosing immune disorders specific to aberrant T-cell receptor activity represents a "real world" context of use. Since such a method of treatment necessarily encompasses specific diseases or disorders exemplified in Applicants specification, including for example, T-cell tumors, lymphomas, leukemias and thymomas, among others, Applicants point out that such a utility represents a "substantial" utility in accordance with the Revised Interim Utility Guidelines. The Guidelines that a method of treating a disorder represents a substantial utility unless the method does not specify the disease or condition to be treated. However, since Applicants specification describes specific diseases or disorders that hSLAP-2 would be useful in treating, the "substantial utility" criterion has been met. Applicants request that the utility rejection be withdrawn in acknowledgement of this guidance.

Applicants also pointed out that the utility of hSLAP-2 is "credible" since one skilled in the art would clearly appreciate that hSLAP-2 is a new member of the SLAP family of adaptor proteins and would be expected to have the asserted utilities based upon the teachings of Applicants specification. The issue of whether such asserted utilities are "credible" is moot in consideration of the independent corroborating support provided by Ms. Whitney's experimental results, Pandey, Holland, and Loreto. Applicants again point the Examiner to the guidance provided by the Revised Interim Utility Guidelines which state that an "assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion". Since the asserted utilities were independently corroborated by Ms. Whitney and three separate post-filing publications, Applicants adamantly assert that the "logic underlying the assertion" is clearly not flawed, nor are the facts flawed, since each of these publications support the teachings of Applicants application as originally filed relative to the hSLAP-2 representing a new member of the SLAP family of adaptors proteins, in addition to its role as a negative regulator of T-cell receptor activation. Applicants request that the utility rejection be withdrawn in acknowledgement of this guidance.

Although Applicants firmly believe that the Examiners utility rejection has been overcome, Applicants would also like to refer the Examiner to the further teachings of McGlade. The teachings

of McGlade are consistent with the teachings of Applicants specification in addition to the teachings of Pandey, Holland, and Loreto, and provide further post-filing publication corroborative evidence that the hSLAP-2 has utility, is in fact a new member of the SLAP family of adaptor proteins, and functions as a negative regulator of T-cell receptor activation. McGlade describes results obtained for a molecule that is 100% identical to hSLAP-2 which they refer to as MARS. McGlade teaches that hSLAP-2 inhibits T-cell receptor mediated NFAT activation (see page 35) which is consistent with its utility as a negative regulator of T-cell receptor activation since NFAT is a transcription factor that is activated by the T-cell receptor and results in transcriptional upregulation and expression of IL-2. McGlade further teaches that hSLAP-2 maps to chromosome 20 in a region that is frequently deleted in myeloproliferative disorders (see page 44), and in particular, premalignant hyperproliferative disorders of the myeloid cell population. McGlade also demonstrated that a cohort of patients with monoallelic deletions of chromosome 20q11 were found to have the hSLAP-2 specifically deleted. The latter finding directly associates the deletion of hSLAP-2 to the incidence of premalignant hyperproliferative disorders of the myeloid cell population. Applicants point out that the latter finding is directly corroborative with the teachings of Applicants specification relative to the utility of hSLAP-2 (see arguments presented *supra*, the arguments presented in Applicants August 18th, 2003 Reply, in addition to the utilities asserted in paragraphs 9, 12, 54, and 76 of Applicants specification). Applicants adamantly assert that hSLAP-2 adequately satisfies all tenets of the utility requirement and request that the utility rejection be withdrawn.

In consideration of the fact that: (a) the requisite teachings demonstrating that hSLAP-2 is a new member of the SLAP family of adaptor proteins is found within Applicants specification as originally filed; (b) the fact that the description of the anticipated function and utility of hSLAP-2 is found within Applicants specification as originally filed (e.g., "negative regulator[s] of intracellular signal transduction in several cell types, including T-cells"); (c) the fact that Applicants specification described one of the ligands for hSLAP-2 (e.g., ZAP-70); (d) the fact that modulation of ZAP-70 is directly linked to the asserted negative T-cell receptor activation utility of hSLAP-2; (e) the fact that T-cell receptor activation is controlled by the co-stimulatory pathway; (e) the fact that disruption of the co-stimulatory pathway is a well-established mechanism for treating immune (e.g., Tan, Webb, Finck, Kremer, etc.) and oncology (e.g., Leach, etc.) diseases and disorders; (f) the fact that negative regulation of T-cell receptor activation is known in the art to lead to T-cell tumors, lymphomas, leukemias, thyomas, and other proliferative conditions; and (g) the fact that four independent groups,

namely Pandey, Holland, Loreto, and McGlade, published papers confirming that hSLAP-2 is a new member of the SLAP family of adaptor proteins, has the same physiological function, and functions via the same mechanism as taught in Applicants specification as originally filed; and (h) Ms. Whitney's experimental results regarding hSLAP-2 modulation of T-cell activity, supports Applicants arguments that hSLAP-2 has a specific, substantial, and credible or well-established utility and that the Examiners maintenance of the utility rejection for the pending claims is erroneous and should be withdrawn.

V. Conclusion

In view of the above remarks and amendments, Applicants respectfully submit that the application is considered to be in good and proper form for allowance and requests that the Examiner pass this application to issue. If the Examiner believes that a telephone conference would expedite the prosecution of this application, the Examiner is invited to call the Applicants' undersigned representative.

Respectfully submitted,

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